Journal of Steroid Biochemistry & Molecular Biology 142 (2014) 48–51

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Review

The "newer" progestogens and postmenopausal hormone therapy (HRT)

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ARTICLE INFO

Article history:
Received 17 July 2013
Received in revised form
26 November 2013
Accepted 4 December 2013
Available online 12 December 2013

Keywords:
Progestogen
Dienogest
Drospirenone
Nomegestrol acetate

ABSTRACT

After a worldwide breakdown of hormone therapy [HT] following the publications of the Women's Health Initiative trial and Million Women's Study in 2002–2003, there is now a trend to turn attention again to HT and to explore particular progestogens, which have been discredited with respect to their side effects. The progestogens to be considered should control undue proliferation of the endometrium and should not interfere negatively with the positive effects of estradiol, regarding carbohydrate and lipid metabolism as well as hemostasis. In the present review, three "newer progestogens" are scrutinized regarding their various actions, in combination with estradiol; the progestogens include dienogest, drospirenone and nomegestrol acetate.

This article is part of a special issue entitled Menopause.

Contents

Introduction

Hormone replacement therapy (HT) was exposed to a dramatic impact by the publications of the Women's Health Initiative (WHI) trial in 2002 [1] and the Million Women Study (MWS) [2] in 2003, affecting women's attitudes and physicians' prescribing practice throughout the world. This caused a general decrease of HT use. Publications that raised a word of caution about discontinuing use of HT were disregarded [3]. Now, over 10 years after the first publication [1] there appears to be a revival or renaissance of HT, which seems to involve publications in leading medical journals [4,5] and outstanding worldwide organizations such as the International Menopause Society and the Endocrine Society.

It is now realized more and more that proper HT contributes to the well-being and function of women who have lost their ovarian function, improves or maintains physical and mental activity, and contributes to the quality of life [6]. This is mainly determined by estrogens. In order to avoid undue chronic stimulatory effects on the endometrium, control menstrual bleeding, avoid abnormal bleeding and avoid cancer development, the combination of the estrogen with a progestogen is needed. The present review will discuss some of the "newer" progestogens used for HT regarding their quality and effectiveness to uphold the favorable effects of estrogens and avoid undue proliferation at the endometrium, with risk of abnormal uterine bleeding (AUB) and oncological problems. The progestogens that will be discussed include dienogest (DNG), drospirenone (DRSP) and nomegestrol acetate (NOMAC).

"Newer" progestogens

Previously the question was raised regarding whether or not progestogens should be selected for HT use [7]. The answer was yes. Therefore, "newer" progestogens should be scrutinized,

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0960-0760/$ – see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.jsbmb.2013.12.003

Table 1
Classification of progestogens.

(1) Progesterone
(2) Retro-progesterone (dydrogesterone)
(3) Progesterone derivatives
(a) 17α-Hydroxyprogesterone derivatives (pregnanes)
• 17α-Hydroxyprogesterone caproate
• 17α-Hydroxyprogesterone heptanoate
• Chlormadinone acetate
• Medroxyprogesterone acetate
• Cyproterone acetate
(b) 19-Norprogesterone derivatives (nor-pregnanes)
• Nomegestrol acetate
• Demegestone
• Promegestone
• Trimegestone
• Nesterone
(4) Testosterone derivatives
(a) 19-Nortestosterone derivatives (estranes)
• Lynestrenol
• Levonorgestrel
• Norethisterone/norethisterone acetate
• Ethynodiol diacetate
• Norgestrinone
• Dienogest
(b) 19-nortestosterone derivatives (19-ethylgonanes)
• Levonorgestrel/norgestrel
• Desogestrel/etonogestrel
• Gestodene
• Norgestimate/norelgestromin
(5) Spirolactone derivatives
• Drospirenone

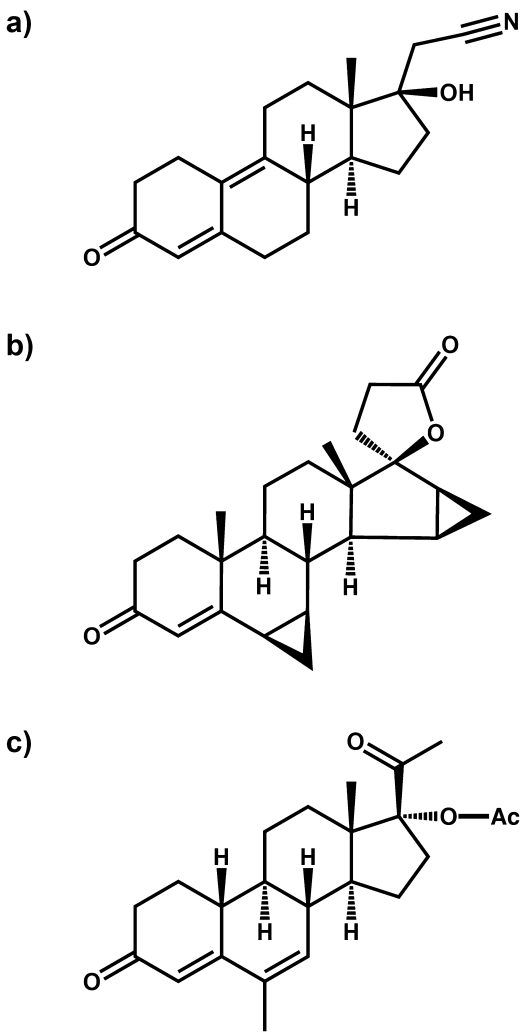

Fig. 1. Chemical structures of the "newer" progestogens dienogest (a), drospirenone (b) and nomegestrol acetate (c).

whether they are qualified to be considered for HT. One has to be aware that all progestogens are not equal. Besides progesterone, which is naturally produced in women in the ovaries (particularly the corpus luteum), in the placenta and to a certain extend in the adrenals, there are a variety of synthetic progestogens [Table 1]. One of these progestogens, dydrogesterone, is a retro-progesterone, and another, DRSP, is spironolactone derivative. We can then subdivide the rest of the progestogens on the basis of those that are related in chemical structure to progesterone and those structurally related to testosterone. The former group can be subdivided into 17α-hydroxyprogesterone derivatives and 19-norprogesterone derivatives, whereas the latter group (19-nortestosterone derivatives) can be divided into estranes and 13-ethylgonanes. The properties of the 17α-hydroxyprogesterone derivatives include mainly peripheral action, relatively moderate inhibition of gonadotropins, antiandrogenic effects, and good tolerability. Properties of 19-nortestosterone derivatives include high bioavailability and strong progestational effects on the endometrium.

Dienogest (DNG)

Dienogest is a 19-nortestosterone derivative with two special structural changes [Fig. 1a]: [a] At the cabon-17 position there is a cyanomethyl group instead of an ethinyl group; [b] A double bond is present between carbons 9 and 10. DNG is the only progestogen that combines properties of both 17α-hydroxyprogesterone and 19-nortestosterone derivatives [8,9].

Dienogest is rapidly and almost completely absorbed, leading to a bioavailability of 90%; about 10% of DNG is free. Approximately 90% of DNG is bound to plasma albumin with no binding to SHBG or CBG. Metabolism of DNG by hydroxylation and conjugation results in inactive metabolites. Unchanged DNG is dominant due to the rapid excretion of its metabolites [23].

The plasma half-life of DNG is approximately 10 h. The steady-state is reached after two to three days and is not influenced by SHBG levels. There is no relevant accumulation of DNG [9]. The use of 20 mg DNG orally daily for 24 weeks does not negatively influence lipid and carbohydrate metabolism, liver enzymes or hemostasis [10]. Evaluating the antiandrogenic effect of DNG it was estimated that it has about 30% to 40% of the antiandrogenic potency of cyproterone acetate, the most potent antiandrogenic progestin [8,9,24].

The important effect of a progestogen is to transfer a proliferative endometrium into a secretory state. The strong progestational effect of DNG on the endometrium has been demonstrated in clinical studies controlling endometrial safety by endometrial biopsy in postmenopausal women treated with estrogen in combination with DNG. When comparing estradiol valerate/DNG with estradiol/norethisterone acetate over twelve cycles,